JACC Vol. 17, No. 3
March 1, 1991:590–8

COOPERATIVE STUDIES

Digoxin Immune Fab Therapy in the Management of Digitalis Intoxication: Safety and Efficacy Results of an Observational Surveillance Study

ANNE R. HICKEY, MS, THOMAS L. WENGER, MD, FACC, VINCENT P. CARPENTER, MS, HUGH H. TILSON, MD, DrPH, MARK A. HLATKY, MD, FACC,* CURT D. FURBERG, MD,† CHARLES H. KIRKPATRICK, MD,‡ HAROLD C. STRAUSS, MD,§ THOMAS W. SMITH, MD, FACC‖

Research Triangle Park, Durham, Winston-Salem, North Carolina; Denver, Colorado; Boston, Massachusetts

An observational surveillance study was conducted to monitor the safety and effectiveness of treatment with Digoxin Immune Fab (Ovine) (Digibind) in patients with digitalis intoxication. Before April 1986, a relatively limited number of patients received treatment with digoxin-specific Fab fragments through a multicenter clinical trial. Beginning with commercial availability in July 1986, this study sought additional, voluntarily reported clinical data pertaining to treatment through a 3 week follow-up.

The study included 717 adults who received Digoxin Immune Fab (Ovine). Most patients were ≥70 years old and developed toxicity during maintenance dosing with digoxin. Fifty percent of patients were reported to have a complete response to treatment, 24% a partial response and 12% no response. The response for 14% of patients was not reported or reported as uncertain. Six patients (0.8%, 95% confidence interval 0.3% to 1.8%) had an allergic reaction to digoxin-specific antibody fragments. Three of the six had a history of allergy to antibiotic drugs. Twenty patients (2.8%, 95% confidence interval 1.7% to 4.3%) developed recrudescent toxicity. Risk of recrudescent toxicity increased sixfold when <50% of the estimated dose of antibody was administered. A total of 215 patients experienced posttreatment adverse events. The events for 163 patients (76%) were judged to result from manifestations of underlying disease and thus considered unrelated to Fab treatment.

Digoxin-specific antibody fragments were generally well tolerated and clinically effective in patients judged by treating physicians to have potentially life-threatening digitalis intoxication.

(J Am Coll Cardiol 1991;17:590–8)

Antibodies have been used to treat the injurious effects of natural toxins for many years. More recently, immunotherapies have been developed to manage drug-induced toxicity (1,2). In the case of life-threatening digitalis intoxication resulting from massive ingestion, antibody therapy has been shown to be particularly valuable because clinical benefit from conventional therapies is limited (3).

Digoxin-specific antibodies were first produced in 1967 (4) and initially used in quantitative assays of digoxin in human serum (5). Their therapeutic potential was subsequently demonstrated by successful prevention and reversal of the toxic effects of digitalis in rabbits and dogs (6,7). Antibody therapy appears to reverse toxicity by binding extracellular digoxin, resulting in a concentration gradient that permits the release and binding to high affinity Fab fragments of membrane-bound digoxin (8).

Concerns regarding the potential for adverse immunologic responses to whole exogenous antibody led to the development of affinity chromatographic techniques for isolating purified digoxin-specific antibody fragments (9). The antibodies are harvested from the serum of hyperimmunized sheep, precipitated as a crude protein fraction with octanoic acid, digested with papain and purified on a ouabain-sepharose affinity gel. Eluates containing digoxin-specific Fab fragments are dialyzed before blending, final formulation and lyophilization.

In baboons and rabbits the immunologic response to the purified Fab fragments was of lesser magnitude and later

From the Medical Division, Burroughs Wellcome Co., Research Triangle Park, North Carolina; *Cardiovascular Division, Department of Medicine, Duke University Medical Center, Durham, North Carolina (current address: Division of Health Services Research, Stanford University School of Medicine, Stanford, California); †Department of Public Health Sciences, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. ‡Division of Clinical Immunology, Department of Medicine, University of Colorado School of Medicine, Division of Allergy and Clinical Immunology, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado; §Departments of Medicine and Pharmacology, Duke University Medical Center, Durham, North Carolina; ‖Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. This study was conducted and funded by the Burroughs Wellcome Co.

Manuscript received May 16, 1990; revised manuscript received September 19, 1990, accepted October 1, 1990.

Address for correspondence: Thomas W. Smith, MD, Cardiovascular Division, Brigham and Women's Hospital, Professor of Medicine, Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115.

Address for reprints: Anne R. Hickey, Epidemiology Section, Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, North Carolina 27709.

0735-1097/91/$3.50

onset than that produced by intact immunogammaglobulin (IgG) (10). In addition, the smaller Fab fragments (50,000 d) were more rapidly distributed and eliminated than IgG (150,000 d) (9). Digoxin-specific Fab fragments were also capable of reversing preexisting effects of digitalis in vitro and in vivo. Reversal of toxicity was more rapid with Fab fragments than with IgG fractions (11). The positive inotropic effects of digoxin, as well as the toxic effects, were reversed (12).

Clinical use of digoxin-specific Fab fragments to treat life-threatening digitalis toxicity was first reported in 1976 (13). The clear clinical benefit in this and similar cases led to the initiation of a multicenter clinical trial to evaluate the safety and effectiveness of ovine digoxin-specific Fab fragments in the treatment of advanced digitalis toxicity (14, 15). At the conclusion of this trial 150 patients had received treatment with digoxin-specific Fab fragments (16). Half of the patients treated had developed toxicity during maintenance therapy with digoxin and most patients had a rapid response to antibody therapy. No allergic responses were detected. Two patients experienced recrudescent digitalis intoxication after response to an inadequate dose of digoxin-specific Fab fragments. Neither of these patients had renal failure, which could be an important risk factor for recrudescence.

The product license for Digoxin Immune Fab (Ovine) (Digibind) (hereafter referred to as Fab) was granted by the Food and Drug Administration in April 1986. At that time there were few data available regarding the immunogenic potential of Fab in clinical use, the populations at highest risk for an allergic response or the immunogenic effects of readministering the antibody fragments for subsequent episodes of toxicity. Similarly, the circumstances in which Fab would be used outside of the clinical trial setting were unknown.

We undertook a postmarketing surveillance study to further evaluate safety and effectiveness of treatment with Fab. The specific objectives of this study were to 1) quantitate any risk of allergic response after initial and subsequent treatments with Fab, 2) identify any serious but infrequent adverse events that may not have been detected in the multicenter clinical trial, 3) assess clinical response or nonresponse to treatment, and 4) characterize the patients and the nature of the toxicity treated with Fab.

Methods

Study protocol. This United States study was observational and relied on the voluntary participation of numerous hospital pharmacists, nurses and physicians. The participation of all United States hospitals was sought. To monitor as many treatments as possible per center, hospital pharmacies were asked to initiate data collection at their institution. When Fab was requested from the pharmacy, pharmacists completed the dispensing section of each form, then provided both the Fab and the form to the treating physician. Treating physicians completed the remainder of the form and sent it to the Project Office at Burroughs Wellcome Co., which maintained the study data. The portion of the form completed by clinicians requested patient demographic data, a brief medical history including allergies or asthma, assumed cause of the digitalis toxicity, pretreatment laboratory values, signs of digitalis toxicity before Fab treatment, other treatments administered before Fab, amount of Fab administered and outcome of treatment including adverse events. A follow-up form was sent directly from the Project Office to the reporting physician to obtain information on the patient's clinical course during the 3 weeks after treatment. Three weeks was the minimal amount of follow-up time deemed necessary to monitor any occurrence of Fab-induced serum sickness. The follow-up form requested information on any additional posttreatment adverse events irrespective of attribution, including recrudescent digitalis toxicity and complications with readministration of digitalis. At no time were patient names requested. Treating physicians used their own clinical judgment in managing the episode of toxicity. The study protocol did not require assessments, interventions or laboratory tests but did ask clinicians to report the results of such evaluations, if performed. An observational design was selected so that findings would reflect the general clinical experience with Fab. The study was overseen by an independent medical advisory panel (C.D.F, C.H.K., H.C.S., T.W.S.) that met regularly throughout the study to evaluate the design and progress and review the findings.

In some cases evaluation of patient response to treatment and cause of adverse events was especially difficult because of the severity of the underlying disease, the limited ability to determine whether the patient had true digitalis intoxication (and thus if Fab could have been expected to have an effect) and the lack of a suitable control group for comparison. Because the cases were complex, all adverse events and reports of nonresponse to treatment were evaluated by a single cardiologist who was not a member of the advisory panel but who served as an independent medical reviewer (M.A.H.). The reviewer systematically assessed the likelihood that an event was attributable to Fab or a result of underlying disease or recrudescent toxicity. Cases of nonresponse were reviewed to determine the possible reasons for nonresponse.

Statistical analysis. Confidence intervals for proportions were based on the binomial distribution. Univariate statistical tests on categorical variables included Fisher's exact test and the chi-square test for homogeneity. Multivariate logistic regression analysis was performed with the LOGIST procedure in SAS (17).

Results

Enrollment and patient follow-up. A total of 717 adult treatments occurring at 487 hospitals were reported to the Project Office. Ninety-one percent of the hospitals were

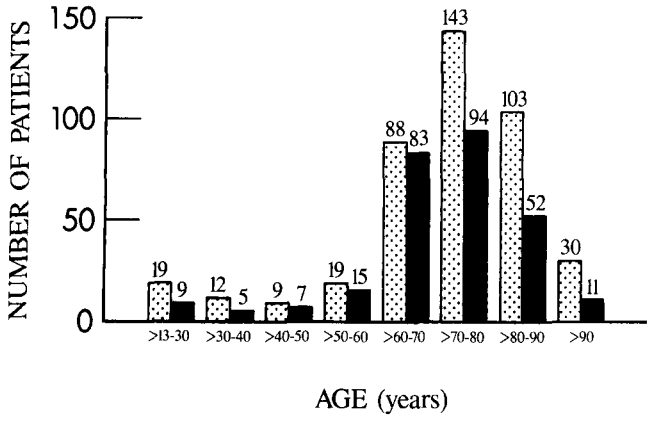

Figure 1. Distribution of age of 717 patients by gender (N = 717). **Dotted bars** = women; **solid bars** = men. Age not specified: 14 patients (7 women, 7 men); gender not specified: 2 patients (68 and 81 years); age and gender not specified: 2 patients.

university affiliated or were tertiary care facilities. Reports on the treatment of 28 children were also received. Data on these cases were analyzed separately and will be presented in a subsequent report. Follow-up forms were received for 75% of the 676 adults alive at the time the initial form was completed. With one exception, all patients were treated for only one episode of toxicity. On the basis of sales data, amount of Fab stocked by each hospital and the distribution of doses administered to patients in this study, an estimated 5,000 treatments occurred in the United States during the 2 year term of the study. Therefore, data were reported on approximately 15% of all treatments.

Patient demographics. Of the 717 patients, 430 (60%) were women and 283 (40%) were men. The gender of four patients was not reported. More than 60% of patients were >70 years old (Fig. 1). The median age was 75 years for women and 72 years for men.

Adult clinical history: impaired renal function. Most patients (94%) were reported as having an underlying cardiovascular disorder. Approximately 32% of all patients had severe impairment of renal function, 35% moderate impairment and 8% mild impairment as determined by estimating the rate of creatinine clearance in ml/min per 70 kg based on age, gender and serum creatinine (18). We defined severe renal impairment as a clearance of <25 ml/min per 70 kg, moderate impairment ≥25 to <50 (women) or ≥25 to <60 (men) and mild impairment ≥50 to <75 (women) or ≥60 to <85 (men). An additional 39 patients for whom the estimated creatinine clearance could not be determined but whose serum creatinine exceeded 1.5 mg/dl were categorized as having mild (n = 7), moderate (n = 22) or severe (n = 10) renal impairment based on reported clinical information.

History of allergy or asthma. This was specifically requested on the data form and 82 patients (11%) were reported to have such a history. Patients were allergic to antibiotics (n = 35), other drugs (n = 19), foods (n = 3) and pollens (n = 2); the specific allergy was not reported for 12 patients. Eleven patients had a history of asthma. None of these 82 patients underwent skin testing (intradermal or prick) for Fab sensitivity before treatment. Twenty of the remaining 635 patients underwent skin testing before treatment with Fab: of these, 19 patients had no reaction to the skin test and 1 patient had an equivocal reaction but no sign of an allergic response after treatment with Fab.

Type of dosing resulting in digitalis intoxication. The dose of digoxin administered and serum digoxin concentrations are summarized in Table 1. Most patients were on maintenance therapy and were taking conventional doses of digoxin. Severe renal impairment was more common in patients with toxicity during maintenance therapy (40%) or after loading doses (38%) than in patients with a single overdose (7%). Single overdoses included both accidental and suicidal

Table 1. Amount of Digoxin Ingested and Serum Digoxin Level by Type of Dosing in 717 Patients*

			Amount Ingested (mg/day or mg) Percentiles of the Distribution				Serum Concentration† (ng/ml) Percentiles of the Distribution			
Type of Dosing	No.	%	No. With Amount Specified	10%	Median	90%	No. With Amount Specified	10%	Median	90%
Maintenance	508	71	419	0.13	0.25	0.25	492	2.5‡	4.2	8
Loading or in-hospital treatment	58	8	50	0.25	0.81	1.98	53	2.2§	4.6	9
Single ingestion (patients with heart disease)	85	12	55	1.0	5.0	17.7	83	4‖	9	24
Single ingestion (patients without heart disease)	35	5	22	3.2	10.0	25.0	32	5	11	25
Unknown or unspecified	31	4	—	—	—	—	26	3.7	7	18

*Values for three patients with digitoxin intoxication are excluded; †values exceeding 5 ng/ml were rounded to the nearest integer; ‡27 values <2.0 ng/ml; §one value <2.0 ng/ml; ‖two values <2.0 ng/ml.

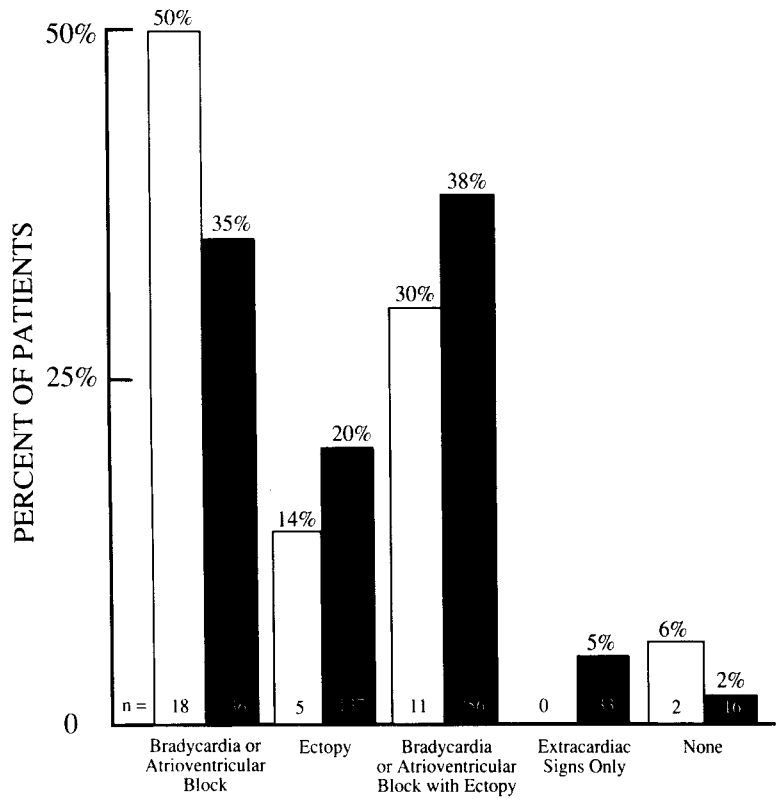

Figure 2. Selected signs of digitalis intoxication in 717 patients by presence or absence of heart disease. **Open bars** = 36 patients without heart disease; **closed bars** = 678 patients with heart disease; presence or absence of heart disease could not be determined for 3 patients.

ingestions. As expected, these patients ingested greater amounts of digoxin and had appreciably higher serum digoxin concentrations than did patients who became intoxicated after therapeutic administrations. The time interval between ingestion of digoxin and sample collection for assay was not requested on data forms.

Signs of digitalis intoxication before treatment with Fab. Physicians were asked to indicate which of 10 specific signs of digitalis intoxication were present before treatment with Fab. Of these specific manifestations, ventricular fibrillation was present in 10%, asystole in 9%, ventricular tachycardia in 20%, hyperkalemia in 26%, third degree atrioventricular (AV) block in 27%, ventricular extrasystoles in 29%, second degree AV block in 14%, supraventricular arrhythmia in 27%, first degree AV block in 17% and nausea or vomiting in 48%. It was not always clear whether the hyperkalemia resulted from renal impairment, severe digitalis intoxication (resulting in substantial inhibition of sodium and potassium transport), or both.

Alternatively, patients were categorized by the presence of ventricular ectopic activity, bradycardia or block, or both, or extracardiac signs only before treatment (Fig. 2). The relative proportions of patients presenting with ventricular ectopic activity, bradycardia or AV block and extracardiac symptoms of digitalis intoxication differed according to the presence or absence of underlying heart disease. Specifically, patients with heart disease were more likely to have ectopic activity with or without a conduction defect than were those without heart disease. However, the effect of variables such as other treatments received before Fab on these relations is unknown.

Treatments received before Fab. Because Fab is indicated for potentially life-threatening digitalis intoxication and was a new therapeutic entity, many other treatments were likely to have been attempted before Fab. Ten percent of patients had received cardiopulmonary resuscitation before treatment with Fab, 9% direct current cardioversion, 18% ventricular pacing, 25% antiarrhythmic drugs, 1% a beta-adrenergic blocking agent and 4% a calcium channel blocking agent. A total of 340 patients (47%) were reported to have received Fab before any other treatment to reverse the toxic episode. The proportion of patients who received Fab before other therapies was similar for those whose toxicity resulted from long-term digoxin therapy and for those with a single overdose.

Dose of Fab administered and response to treatment. Doses administered to adult patients ranged from 8 mg (<1 vial) to 1,600 mg (40 vials). The median dose was 120 mg (three vials) and the most frequently administered dose was 80 mg (two vials). A total of 357 (50%) of the 717 patients were reported to have had a complete reversal of the signs of toxicity, 172 (24%) had partial reversal and 89 (12%) had no response to treatment. The response was not reported or reported as uncertain for 99 patients (14%) (Fig. 3). The relation between adequacy of the dose of Fab administered and the patient's response to treatment was evaluated. An estimated "adequate" dose was calculated based on patient body weight and serum digoxin or digitoxin level for patients

JACC Vol. 17, No. 3
March 1, 1991:590–8

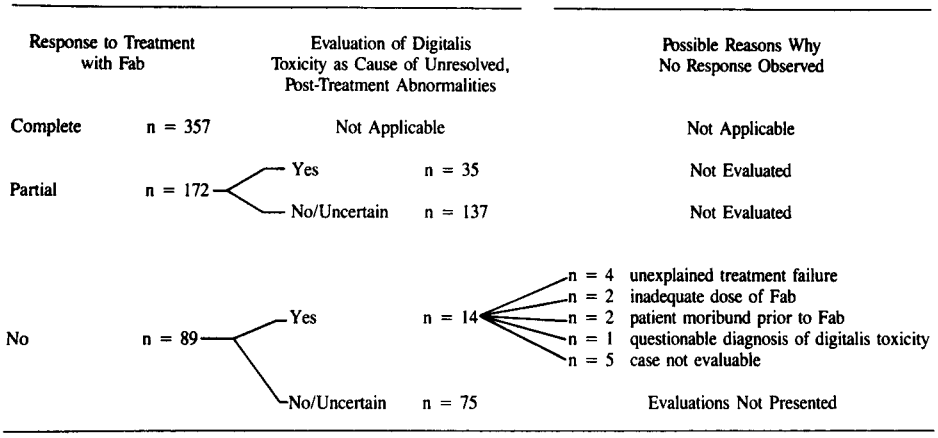

Figure 3. Response of 717 patients to treatment with Fab.

with toxicity from therapeutic administrations and on the amount ingested for those patients with toxicity resulting from a single overdose. Forty-seven patients received <50% of an adequate dose, 69 received 50% to <75%, 155 received 75% to <100% and 359 received ≥100% of the estimated neutralizing dose. No clear relation between initial response to treatment and percent of the estimated adequate dose actually administered was observed.

Nonresponse to Fab was reported for 14% of the patients with toxicity after maintenance dosing, 20% of patients with toxicity after loading doses or in-hospital treatment and 15% of patients with heart disease who ingested a single overdose. In contrast, none of the patients without heart disease who ingested a single overdose were nonresponders to Fab. The differences in response by dose category approached but did not achieve statistical significance, perhaps because of the small number of patients in the group without heart disease. Several patients had relatively mild signs of toxicity or relatively low serum concentrations of digoxin. However, response to Fab did not appear to vary by severity of presenting signs even when persons with serum digoxin concentrations <3.0 ng/ml were excluded from the analysis.

For those patients whose response was reported as less than complete, the form requested that physicians report whether residual abnormalities were still believed to be due to digitalis intoxication (Fig. 3). The abnormalities for 20% of the patients with a partial response and for 16% of those with no response were still believed to be due to digitalis intoxication. The independent cardiologist concluded that four cases represented possible treatment failure. These four cases, as reported by treating clinicians, are described in the Appendix.

Adverse events. The clinical course of 215 patients involved at least one reported adverse medical event at some time after treatment with Fab. Only 52 patients (7%) had an event considered possibly or probably related to the administration of Fab. A total of 171 patients (24%) were reported to have died; none of the deaths were attributed to Fab. Eighty-six deaths (50%) occurred within 2 days and 142 (83%) occurred within 3 weeks after Fab treatment. Events coded as possibly or probably related to Fab by either the reporting clinician or the medical reviewer were categorized into four groups: allergic type responses, possible recrudescent digitalis toxicity, complications associated with readministration of digitalis after Fab treatment and other events (Tables 2 to 4).

Allergic responses (Table 2). Six possible or probable allergic reactions were reported; four occurred on the day of treatment and one each occurred 11 and 16 days after treatment. Three patients developed a pruritic rash on the day of treatment, and one of these also had facial swelling and flushing. The three other possible or probable allergic reactions are less clearly attributable to Fab and included urticaria, thrombocytopenia and an episode of shaking and chills without fever. Two other events, fever and an episode of wheezing and dyspnea, may have represented allergic responses; however, the course of these events appeared to be more consistent with underlying clinical problems than with an allergic reaction. These two cases were not included in the estimated incidence of allergic response.

Thus, 0.8% of patients (6 of 717, 95% confidence interval 0.3% to 1.8%) developed allergic responses during treatment with Fab. The likelihood of allergic response was distinctly greater in patients with a history of allergy or asthma. Of the six allergic responses, four (5%, 95% confidence interval 1.3% to 12%) occurred among the 82 patients with a history of allergy or asthma. Three (9%, 95% confidence interval 1.8% to 23%) were in the subgroup of 35 patients with a history of allergy to antibiotics; all three developed a pruritic rash. The incidence of allergic response in the 635 patients without a history of allergy or asthma was 0.3% (95% confidence interval 0.04% to 1.1%).

Recrudescent toxicity (Table 3). Twenty (2.8%, 95% confidence interval, 1.7% to 4.3%) of the 717 patients experienced an event reported by the treating physician or retrospectively evaluated by the medical reviewer as recrudescent toxicity. Sixteen of the 20 cases recurred within 3 days of the initial treatment with Fab, including 5 that recurred within 12 h. The remaining four patients had recurrence of toxicity from 4 to 11 days after treatment. Five

Table 2. Allergic Responses in Six Patients

Patient	Age (yr)/ Gender	Manifestation	Time of Occurrence Posttreatment	Allergy History	Other Factors Possibly Contributing to Observed Symptoms	Treatment for Reaction	Outcome	Attribution of Event to Fab	
								Reporting Physician	Medical Reviewer
Possible or probable (N =6)									
1	28/F	Total body rash, swelling of eyelids, facial flushing	Before completion of Fab infusion	Penicillin, tetracycline, asthma	None	Fab infusion discontinued and diphenhydramine administered	No further sequelae	Probable	Probable
2	54/F	Urticaria	16 days	Naproxen	Lisinopril on days 11 to 16 post Fab	Terfenadine	No further sequelae	Possible	Possible
3	61/M	Pruritic rash	Same day, time not specified	Penicillin	None	Unspecified medication	No further sequelae	Possible	Probable
4	63/F	Shaking, chills (afebrile)	1.5 h	None	Diabetes, rehydration day before Fab	Diphenhydramine, hydrocortisone	No further sequelae	Probable	Possible
5	64/F	Pruritic rash	30 min	Cefaclor	None	Hydrocortisone	No further sequelae	Probable	Probable
6	73/F	Thrombocytopenia (7,000/mm^3)	11 days	None	Phenytoin, heparin, ranitidine, dipyridamole, isosorbide dinitrate	Prolonged hospitalization	No further sequelae	Possible	Possible
Uncertain (N = 2)									
a	70/M	Fever (T° = 107)	1 h post; T° = 104; peak 8 h post; T° = 107; fever continued for 2 days	Not specified	Theophylline toxicity, possible severe alcohol withdrawal, possible malignant hyperthermia	Cooling blankets, fluids (cultures negative)	Patient died of severe metabolic acidosis 2 days after treatment	Possible	Possible
b	82/M	Wheezing, dyspnea	2 days	None	Congestive heart failure, pulmonary metastases secondary to prostate cancer, transfusion following Fab	Not specified	Patient died of underlying heart disease approximately 2 weeks later	Possible	Unlikely

of the six patients given additional Fab for recurrent toxicity had complete reversal of the recurrent toxicity and the sixth had a partial response to the second administration of Fab.

Recrudescent toxicity was more frequent among persons receiving less than the estimated adequate dose of Fab. Of the 47 patients who received <50% of the estimated dose, 4 (8.5%) had recurrence of toxicity compared with 4 (5.8%) of the 69 who received 50% to <75%, 4 (2.6%) of the 155 who received 75% to <100% and 8 (2.2%) of the 359 who received a full neutralizing dose.

Inadequacy of the initial dose was the only factor associated with recrudescent digitalis toxicity in a multivariate logistic regression analysis that also included variables representing renal function and response to Fab treatment. The risk of recrudescent toxicity in persons receiving <50% of the estimated adequate dose was 5.8 (95% confidence interval 3.7 to 9.0) times greater than that of persons receiving 100% of the adequate dose. The relative risk for patients receiving 50% to <75% was 3.2 (95% confidence interval 2.0 to 5.0) and that of patients receiving 75% to <100% of the adequate dose was 1.8 (95% confidence interval 1.1 to 2.8) times that of patients receiving 100% of the estimated adequate dose.

Complications with readministration of digitalis. One hundred twenty-nine patients resumed digitalis therapy a median of 7 days (25% within 4 days, 75% within 13 days) after treatment with Fab. Two patients developed a rapid ventricular response to atrial fibrillation after Fab treatment. The ventricular response was not controlled by digoxin administered 1 day (one patient) and 4 days (one patient) after treatment with Fab.

Other adverse events (Table 4). Twenty-six patients experienced an event other than an allergic response, recrudescent digitalis toxicity or complication of readministration of digitalis that either the reporting physician or medical reviewer considered possibly or probably related to treatment with Fab. Fourteen patients had an adverse cardiovascular event that the medical reviewer judged was due to incomplete response to Fab treatment (n = 4), the patients' moribund status before treatment with death occurring shortly after treatment (n = 2) and withdrawal of inotropic effect of digitalis (n = 5). Events experienced by the latter group included pulmonary edema, hypotension with decreasing cardiac output, congestive heart failure, congestive heart failure with left ventricular dilation and electromechanical dissociation. A possible relation between Fab treatment and premature ventricular complexes in another patient could not be ruled out. The medical reviewer judged the events experienced by the two remaining patients as unrelated to Fab. Noncardiovascular adverse events were infrequent and generally attributable to underlying disease or concomitant therapy.

Retreatment with Fab. Only one patient was reported to have been treated with Fab for more than one episode of digitalis toxicity. A 42 year old woman was treated twice approximately 2 months apart. In both instances toxicity

Table 3. Summary of 20 Cases of Recrudescent Digitalis Intoxication

Manifestation	Age (yr)/ Gender	Pretreatment Renal Impairment	Estimated Adequate Dose Administered (%)	Posttreatment Interval Before Recurrence	Response to Initial Fab Treatment	Assessments of Manifestations as Signs of Recrudescent Toxicity*	
						Reporting Physician	Medical Reviewer
Atrioventricular block							
(n = 5)	30/F	No	13	8 h	Complete	Yes	Probable
	36/F	No	47	7 h	Partial	Yes	Unlikely
	78/F	No	60	10 h	Partial	Yes	Probable
	81/F	Moderate	81	7 days	Not specified	Yes	Possible
	91/F	Moderate	>100	2 days	Complete	Yes	Possible
Ventricular arrhythmia							
(n = 7)	44/F	Mild	>100	2 days	Complete	Yes	Unlikely
	47/F	Severe	>100	15 h	Partial	Yes	Unlikely
	56/F	No	60	3 days	Partial	Yes	Possible
	64/F	Severe	66	2 days	Complete	Yes	Possible
	64/F	Severe	>100	20 h	Partial	Yes	Unlikely
	67/F	Severe	100	5 days	Complete	No	Possible
	78/F	Moderate	>100	3 days	Complete	Yes	Possible
Asystole							
(n = 3)	71/F	Severe	100	11 days	Complete	Yes	Possible
	74/F	Severe	78	1 day	Complete	Yes	Possible
	79/M	Severe	43	12 h	Partial	No	Possible
Not specified							
(n = 5)	79/F	Severe	85	1 h	Partial	Yes	Unlikely†
	81/M	Unknown	>100	4 days	Complete	Yes	Possible
	83/M	Unknown	84	2.5 days	Partial	Yes	Possible
	84/M	Severe	71	1 day	Complete	Yes	Possible
	87/F	Severe	46	2 days	Partial	Yes	Possible

*Reporting physicians coded either yes or no; the medical reviewer coded unlikely, possible or probable; †considered to be a single episode of toxicity rather than recrudescent toxicity based on partial response and short interval before reported recrudescence of toxicity.

Table 4. "Other" Adverse Events in 26 Patients

	No. of Patients	Number of Events Attributed to Fab Treatment*	
		Reporting Physician	Medical Reviewer
Cardiovascular disorders	14		
Atrioventricular block	1	0	1
Ventricular arrhythmia	4	3	3
Asystole	5	3	2
Congestive heart failure	4	4	4
Urologic disorders	3		
Renal failure (resolved with ↑ heart rate)	1	1	0
Acute tubular necrosis (history of urogenital cancer, nephrectomy)	1	1	0
Hematuria	1	1	0
Gastrointestinal disorders	3		
Increasing hepatic enzymes, jaundice (postoperative patient)	1	0	1
Diarrhea (history of Crohn's disease)	1	1	0
Nausea	1	1	0
Metabolic disorders	6		
Hyperkalemia (2 patients treated concurrently with potassium)	3	3	1
Hypokalemia	2	2	1
Hypoglycemia	1	1	1

*Attribution of possible or probable by either reporting clinician or medical reviewer. Events attributed to Fab by the medical reviewer include those resulting from incomplete response and withdrawal of inotropic effect of digitalis.

resulted from suicidal overdose attempts, the first with 7.5 mg digoxin and the second with 6.25 mg digoxin. The patient received 320 mg Fab in the first treatment and 360 mg in the second and responded to both treatments. No adverse events were reported in association with either treatment.

Discussion

Comparison with results of multicenter clinical trial. This observational study extends the reported clinical experience with heterologous, digoxin-specific antibody fragments of ovine origin in persons with potentially life-threatening digitalis intoxication. Unlike the multicenter trial (14–16) that preceded this study, in which there were many younger patients with suicidal ingestions of digitalis, the majority of patients in this study were >70 years old, had underlying heart disease and developed digitalis intoxication during long-term maintenance therapy. However, overall favorable response to Fab and a low incidence of treatment-related adverse events were found in both studies. In the present study, complete or partial reversal of toxicity was reported for 75% of all patients or 86% of those for whom a response was specified. In the multicenter trial (16) a complete resolution of signs and symptoms of toxicity was observed in 119 (80%) and improvement in 14 (10%). Seven percent of our patients were reported to have experienced an adverse event compared with 9% of the 150 patients treated in the multicenter trial.

Response to Fab treatment. When presumed digitalis toxicity did not respond to treatment, incorrect diagnosis of digitalis toxicity, inadequate doses of Fab and presence of a moribund state before treatment may have contributed to nonresponse. Attempts to discern a dose-related lack of response were unsuccessful, perhaps owing to variability in physicians' assessments of response and in the accuracy of diagnoses and estimated adequate doses of Fab based on nonsteady state serum digoxin concentrations. Reported response was found to vary by presence or absence of heart disease. Percent response was highest for those patients without a history of heart disease who ingested a single overdose of digoxin. This finding could have resulted from increased accuracy of the diagnosis of digitalis intoxication or the absence of confounding cardiac abnormalities caused by underlying disease in these patients.

Recrudescent digitalis intoxication. Approximately 3% of patients developed recrudescent digitalis intoxication. Eighty percent of the cases of recrudescent toxicity occurred within 3 days of the initial treatment with Fab; however, one case occurred as late as 11 days after treatment with Fab. Inadequacy of the initial dose of Fab appeared to be predictive of recrudescent toxicity, whereas completeness of response to the initial dose and pretreatment renal function did not. The risk of recrudescence was six times more likely in patients given less than one half of the calculated dose than in patients given a full neutralizing dose. Regardless of dose, recurrence of toxicity was infrequent; even among those patients at highest risk, <9% had recrudescence.

Allergic reactions. At the conclusion of the multicenter trial of Fab (16), no allergic reactions to Fab had been noted; therefore, the incidence of allergic reactions in previously unexposed patients could not be estimated. From this study possible or probable allergic reactions to ovine Fab can be estimated to occur in about 1 of 120 patients treated. The incidence of allergic reactions was higher in patients with a history of allergy to antibiotics; 1 in 12 of these patients experienced an allergic reaction. However, all allergic responses were effectively managed with conventional therapy. This study could not assess the likelihood of an allergic response with subsequent Fab treatment; only one retreatment for a separate episode of toxicity was reported. Further evaluation of the immunogenic potential of Fab in retreatment is needed. In this regard it is of interest that none of the 600 patients who were administered heterologous monoclonal murine antimyosin Fab fragments developed an allergic reaction or a significant increase in antimouse antibody titer after injection (19).

Study limitations. As with any observational study of this nature, there are many limitations that may affect interpretation of these data. First, the nature and frequency of adverse events occurring in patients treated with Fab could not be assessed relative to another similar but untreated group of patients. All cases of nonresponse and adverse events were reviewed by an independent cardiologist to provide additional insight into the cause of events; nevertheless, retrospective review, especially with limited data, can be inconclusive. Second, an estimated 15% of all treatments occurring in the United States within the first 2 years of availability were reported. It is possible that some adverse events related to Fab treatment occur very rarely and therefore were not observed in this study. However, our sample size of 717 adults is sufficient to conclude that such events, if they occur, occur no more frequently than in 4 of 1,000 patients treated. Third, reporting bias could have occurred. Some treatments for suicidal ingestion may have been withheld for reasons of patient confidentiality. Also, it is possible that physicians underreported cases of digitalis toxicity occurring after therapeutic, in-hospital administration of digoxin. We cannot determine the extent to which such bias might have occurred or the possible effects on these findings. The reporting of all treatments was strongly encouraged but no reimbursement was provided. However, we did not observe any differences by cause of the toxic episode in the reported response to treatment or the frequency of allergic responses, recrudescent toxicity or other adverse events of possible attribution to Fab. In addition, the geographic distribution and size of hospitals reporting treatment were comparable with those of hospitals receiving Fab but electing not to report treatment. Bias could have occurred in the reporting of follow-up data; however, percent follow-up of eligible cases was high (76%) and willing-

ness to report follow-up data did not appear to vary by cause of the toxic episode or initial response to treatment.

Conclusions. Despite the potential shortcomings inherent in studies of this type, this data base represents the largest single source of information on human exposure to polyclonal Fab fragments. Many patients in this study were of advanced age with deteriorated clinical status both from life-threatening digitalis intoxication and underlying heart disease. The results from this observational study and those from the multicenter clinical trial suggest that treatment with digoxin-specific antibody fragments provides substantial benefit even in such cases and is associated with a low incidence of treatment-related adverse events. In contrast to previous trials in which no allergic responses and few cases of recrudescent toxicity were seen, allergic response was reported for 0.8% and recrudescent toxicity for 2.8% of the 717 patients in this study. A history of allergy to antibiotics and insufficient initial doses of Fab contributed to the occurrence of allergic responses and recrudescent toxicity, respectively.

We express our gratitude to the many pharmacists, physicians and nurses whose participation made this study possible.

Appendix

Case 1. A 73 year old, 86 kg Asian man with congestive heart failure, chronic obstructive pulmonary disease and bronchial asthma who was receiving quinidine sulfate, 200 mg four times a day, and digoxin, 0.125 mg/day, presented with nausea, vomiting, hyperkalemia, first degree AV block and cardiac arrest according to the clinician's report. He became comatose before Fab treatment. His serum digoxin level was 4.4 ng/ml, serum creatinine 3.6 mg/dl, blood urea nitrogen (BUN) was 30 mg/dl and serum potassium 5.3 mEq/liter. The patient received antiarrhythmic drugs and underwent cardiac pacing before administration of 160 mg of Fab. Nine hours after treatment, the patient was in complete heart block with a junctional rhythm of 52 beats/min and was still deeply comatose. The patient was maintained on a pacemaker. Serum creatinine was 3.7 mg/dl. No follow-up data were reported.

Case 2. An 84 year old, 73 kg white woman with congestive heart failure became digoxin intoxicated as a result of self-misdosing. Nausea and vomiting, bradycardia (heart rate 17 to 30 beats/min), third degree AV block, ventricular extrasystoles and ventricular fibrillation were reported to have occurred before treatment. Serum digoxin concentration was 9.8 ng/ml, blood urea nitrogen 23 mg/dl, serum creatinine 1.6 mg/dl and serum potassium 5.3 mEq/liter. The patient received 240 mg Fab but continued to have severe bradyarrhythmias requiring pacing. The time course before assessment of response and placement of the pacemaker was not specified. No follow-up data were reported.

Case 3. A 71 year old, 46 kg white woman with congestive heart failure, chronic obstructive pulmonary disease, and recent myocardial infarction became digitalis intoxicated while receiving 0.25 mg/day digoxin. Before treatment she had had nausea, vomiting, supraventricular arrhythmias, first and second degree heart block and ventricular extrasystoles. Serum digoxin concentration was 4.5 ng/ml, blood urea nitrogen 40 mg/dl, serum creatinine 2.0 mg/dl and serum potassium 3.8 mEq/liter. She received 80 mg Fab with no response. The signs of toxicity resolved approximately 5 days later.

Case 4. An 86 year old, 55 kg white woman with a history of seizure disorder and unspecified heart disease was taking maintenance digoxin; however, toxicity resulted from an apparent single overdose of unknown quantity. The patient had also taken an overdose of phenobarbital and an elevated serum phenytoin level of 25 mg/dl was reported. She had had supraventricular arrhythmias, third degree AV block and ventricular extrasystoles before treatment. Her serum digoxin level was 7 ng/ml, blood urea nitrogen 10 mg/dl, serum creatinine 0.7 mg/dl and serum potassium 4.7 mEq/liter. She was administered antiarrhythmic drugs before receiving 280 mg Fab. The third degree AV block persisted for 36 h after treatment, then resolved to first degree AV block.

References

1. Butler VP Jr. Antibodies as specific antagonists of toxins, drugs, and hormones. Pharmacol Rev 1982;34:109–14.
2. Sullivan JB Jr. Immunotherapy in the poisoned patient: overview of present applications and future trends. Medical Toxicology 1986;1:47–60.
3. Smith TW, Willerson JT. Suicidal and accidental digoxin ingestion: report of five cases with serum digoxin level correlations. Circulation 1971;44: 29–36.
4. Butler VP Jr, Chen JP. Digoxin-specific antibodies. Proc Natl Acad Sci 1967;57:71–8.
5. Smith TW, Butler VP Jr, Haber E. Determination of therapeutic and toxic serum digoxin concentrations by radioimmunoassay. N Engl J Med 1969;281:1212–6.
6. Schmidt DH, Butler VP Jr. Immunological protection against digoxin toxicity. J Clin Invest 1971;50:866–71.
7. Schmidt DH, Butler VP Jr. Reversal of digoxin toxicity with specific antibodies. J Clin Invest 1971;50:1738–44.
8. Watson JF, Butler VP Jr. Biologic activity of digoxin-specific antisera. J Clin Invest 1972;51:638–48.
9. Curd J, Smith TW, Jaton J-C, Haber E. The isolation of digoxin-specific antibody and its use in reversing the effects of digoxin. Proc Natl Acad Sci 1971;68:2401–6.
10. Smith TW, Lloyd BL, Spicer N, Haber E. Immunogenicity and kinetics of distribution and elimination of sheep digoxin-specific IgG and Fab fragments in the rabbit and baboon. Clin Exp Immunol 1979;36:384–96.
11. Lloyd BL, Smith TW. Contrasting rates of reversal of digoxin toxicity by digoxin-specific IgG and Fab fragments. Circulation 1978;58:280–3.
12. Ochs HR, Vatner SF, Smith TW. Reversal of inotropic effects of digoxin by specific antibodies and their Fab fragments in the conscious dog. J Pharmacol Exp Ther 1978;207:64–71.
13. Smith TW, Haber E, Yeatman L, Butler VP Jr. Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. N Engl J Med 1976;294:797–800.
14. Smith TW, Butler VP Jr, Haber E, et al. Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. N Engl J Med 1982;307:1357–62.
15. Wenger TL, Butler VP Jr, Haber E, Smith TW. Treatment of 63 severely digitalis-toxic patients with digoxin-specific antibody fragments. J Am Coll Cardiol 1985;5:118A–23A.
16. Antman EM, Wenger TL, Butler VP, Smith TW. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific antibody fragments: final report of a multicenter study. Circulation 1990;81:1744–52.
17. SAS Institute Inc. SUGI Supplemental Library User's Guide. 5th ed. Cary, North Carolina: SAS Institute Inc., 1986:269–93.
18. Mawer EG, Knowles BR, Lucas SB, Stirland RM, Tooth JA. Computer-assisted prescribing of kanamycin for patients with renal insufficiency. Lancet 1972;1:12–5.
19. Johnson LL, Seldin DW. The role of antimyosin antibodies in acute myocardial infarction. Semin Nucl Med 1989;19:238–48.